Prolonged QTc Intervals and Decreased Left Ventricular Contractility in Patients with Propionic Acidemia

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Objective To investigate electrophysiological and functional signs of myocardial damage in patients with propionic acidemia (PA), an inborn error of metabolism caused by deficiency of propionyl CoA carboxylase (PCC).

Study design In an observational longitudinal study 10 patients with PA (6 boys and 4 girls) ranging between 2.5 and 20.2 (median 9.0) years of age at last follow-up were investigated over a period of up to 20 (mean 7.4) years using 12-lead electrocardiograms (ECGs), 24-hour continuous ECG recordings, bicycle exercise testings, and echocardiography with special focus on repolarization abnormalities such as corrected QT interval (QTc) prolongation, ventricular dysrhythmias, and left ventricular systolic function.

Results QTc interval was prolonged (>440 ms) in 70% of patients beyond infanthood. Continuous ECG recordings revealed rhythm disturbances in 20% of patients. M-mode echocardiographic left ventricular function was reduced (fractional shortening [FS] <30%) in 40%. One patient showed signs of dilated cardiomyopathy.

Conclusions The majority of patients with PA (even in clinically stable situations) have disturbances in cardiac electrophysiology that can contribute to cardiac complications. Possible mechanisms include effects of toxic metabolites or deprivation of essential substrates. To avoid life-threatening complications, we recommend regular cardiological evaluations in this group of patients. *(J Pediatr 2007;150:192-7)*

Propionic acidemia (PA) is a recessive disorder caused by a deficiency of propionyl CoA carboxylase (PCC), an enzyme involved in the catabolism of valine, isoleucine, methionine, threonine, cholesterol and odd-carbon numbered fatty acids, thymine, and uracil.[1] Mutations of both the *PCCA* gene mapped to chromosome 13q32 and the *PCCB* gene mapped to chromosome 3q13.3-q22 have been described.[2,3] Accumulating propionyl-CoA or its metabolites may result in hypoglycemia, hyperammonemia, and hyperglycinemia.[4-6] Different long-term complications occur and involve mainly the central nervous system, feeding difficulties, and metabolic crises in catabolic situations.[7,8] Because of the great genetic heterogeneity[2] the clinical picture varies between severe early-onset forms manifesting during the first days of life, and mild late-onset variations, which show first signs during adulthood.

Cardiomyopathy and sudden cardiac death have been described as complications of several metabolic disorders.[9,10] In patients with PA, these life-threatening complications are frequent.[11-15] Deficiencies in carnitine or selenium and acidosis are possible causes. Furthermore, electrophysiological changes such as prolongation of the QT interval, which has been observed in patients with PA,[11,16] can occur in patients with cardiomyopathy and can predispose them to life-threatening ventricular arrhythmias.[11,12] However, electrophysiological changes have not been reported in this patient group.

The aim of this study was to characterize electrocardiographic and echocardiographic changes in patients with PA before to life-threatening arrhythmia or loss of ventricular function.

METHODS

Ten patients with PA followed by our institutions between July 2000 and December 2005 (Department of Pediatrics, Innsbruck Medical University, Austria, 9 patients; Children's Hospital, Private Medical University, Salzburg, Austria, 1 patient) were included in this study. Age ranged between 1 day and 12 months at diagnosis, and

ASD	Atrial septal defect	PCC	Propionyl CoA carboxylase
ECG	Electrocardiogram	QTc	Corrected QT interval
FS	Fractional shortening	VEB	Ventricular ectopic beats
PA	Propionic acidemia		

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between 2.5 and 20.2 (median 9.0) years at the latest follow-up investigation (Table I; available at www.jpeds.com). Time of follow-up ranged between 1.0 and 20.0 (mean 7.4) years. Diagnosis was established on the basis of urinary excretion of the characteristic organic acids in all patients, and it was confirmed by reduced enzymatic activity of PCC in fibroblasts (Dr Regula Baumgartner, Department of Pediatrics, University of Basel, Switzerland) and/or mutational analysis of the *PCCA* and *PCCB* genes in all but one patient (Table I).[2,3,17] Three different homozygous mutations were present. Patients 2 and 3, 4 and 5, 6 and 7, and 8 and 9 are siblings, whereas patients 8 and 9 are cousins of patients 2 and 3. The mutation of patients 1 through 3 and 8 and 9 (reference 3) and of patients 7 and 8 (reference 2) have been published elsewhere.[2,3] In all cases therapy consisted of restricted natural protein intake (1.1 to 1.5 g/kg daily), special amino acid supplementation (free of valine, leucine, methionine, and threonine, to achieve adequate protein intake for age), L-carnitine (50-100 mg/kg body weight/day), and vitamin supplementation. All patients grew well (between 10th and 97th weight percentile). Seizures in patients 4 and 5 were treated with oral valproic acid. Patients 1 and 2 had a history of syncope in their teenage years, which was probably vasodepressor or neurally mediated. Patient 4 had a surgical closure of a secundum atrial septal defect at 8 years of age. Three patients died, after data acquisition for this study was completed: patient 2 at 16 years of age because of a bicycle accident (an underlying syncope cannot be excluded), patient 7 at 6 years of age because of pneumococcal meningitis, and patient 10 at 3 years of age after a prolonged metabolic decompensation.

According to our study protocol, we performed serial clinical investigations during routine follow-up examinations in yearly intervals and in some patients during hospitalization because of metabolic decompensation. All patients and parents gave written informed consent. The study protocol was approved by the institutional committee on human research in Innsbruck.

We evaluated all patients according to our study protocol as described below by standard 12-lead electrocardiography (ECG) and echocardiography on several occasions during yearly routine follow-up. Twenty-four-hour Holter monitoring was performed in all patients at least once; in those with arrhythmias up to seven recordings were done. Exercise testing was performed in five patients, who were appropriate for bicycle ergometry (>6 years of age).

Resting 12-lead ECGs were recorded at a paper speed of 50 mm per second with a Corina recorder (General Electric Medical Systems, Information Technologies, Freiburg, Germany) in supine position. All prospective recordings were digitally stored. One investigator (D.B.) analyzed 2 to 15 (mean 6.8) ECGs per patient, in total, 64 ECGs, 44 of them prospectively. Twenty ECGs, which were registrated before the study started in July 2000, were analyzed retrospectively from paper prints. RR and QT intervals were measured in lead II from five nonconsecutive beats, and the corrected QT interval (QTc) was calculated by dividing the QT interval by the square root of the RR interval (Bazett's formula).[18] Additionally, we performed morphologic analysis of ST intervals, and measurement of QT-interval dispersion, which is defined as the difference between the maximum and minimum QT time occuring in any of the 12 ECG leads, so far it can be reliably measured.[19] For each patient the median QTc interval of all his or her standard ECG recordings (median QTc) as well as the maximum QTc interval of all standard ECG recordings (maximum QTc) and the QT dispersion determined from the first ECG recording during the prospective study period are shown in Table II. Interobserver reproducibility of QT and QTc measurements, calculated as the standard deviation of the difference between measurements and expressed as the percentage of the mean of the measurements, was determined after re-evaluation of randomly selected ECG recordings by a second investigator (U.S.) blinded to the initial results.

Twenty-four-hour continuous ECG recordings were done in all patients at least once (maximum seven recordings per patient) using a Lifecard CF Holter recorder system (Del Mar Reynolds Medical, Hertford, UK). Follow-up recordings were performed in yearly intervals if rhythm disturbances were present. After an initial automatic processing of the data, an experienced observer reviewed the classification of abnormal beats (total number of ventricular ectopic beats [VEB], and total number of VEB occuring in couplets). Besides analysis of rhythm disorders, QTc at maximum heart rate was determined.

In patients >6 years of age, we performed upright, graded exercise testing on an ERG-900 bicycle ergometer (Ergoline, Bitz, Germany). The test protocol scheduled an initial 2-minute period with approximately 0.5 W/kg body weight (15, 20 or 25 W, respectively), followed by increments of 0.5 W/kg body weight every 2 minutes, until exhaustion. Each patient was verbally encouraged to continue exercising until his or her maximum voluntary exercise capacity was attained. After exercise, patients were immediately placed in the supine position to monitor ECG, heart rate, and blood pressure for 10 minutes. QTc was determined before, during exercise at the end of each workload level, and after exercise every 2 minutes for at least 10 minutes until heart rate returned to the resting value. The maximum QTc was selected from these measurements.

All patients underwent a complete transthoracic echocardiographic examination using a System Five echo machine (General Electric Vingmed Ultrasound, Horten, Norway). We performed two-dimensional guided M-mode measurements of the left ventricle to measure cardiac performance according to recommendations of the American Society of Echocardiography[20]; therefore we determined left ventricular end-diastolic, end-systolic, luminal, and wall diameters, and we calculated fractional shortening (FS). Anatomy and function of the mitral and aortic valve were assessed by two-dimensional echocardiography, color flow mapping, and pulsed-wave and continuous-wave Doppler recordings. Cardiomyopathy was classified as dilated on the basis of mor-